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Article title: Fertility, pregnancy and gynecological outcomes after fetoscopic surgery for congenital diaphragmatic hernia

First Author: C. Gregoir

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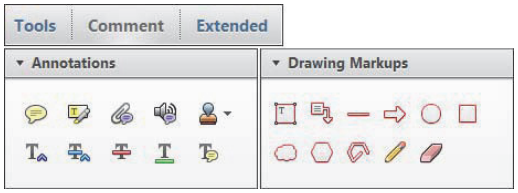

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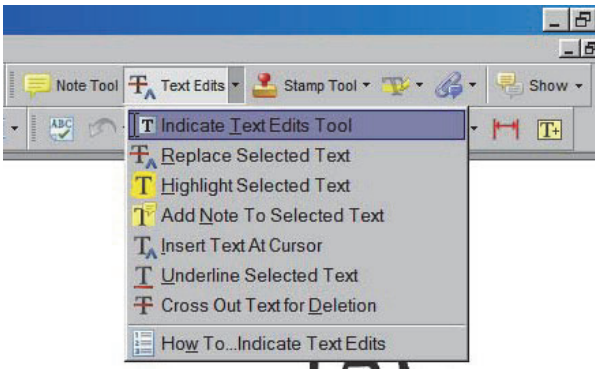

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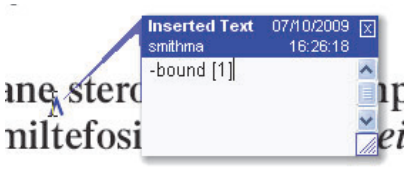

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human reproduction

ORIGINAL ARTICLE *Infertility*

Fertility, pregnancy and gynecological outcomes after fetoscopic surgery for congenital diaphragmatic hernia

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STUDY QUESTION: What is the impact of fetoscopic surgery for isolated Congenital Diaphragmatic Hernia (CDH) on future reproductive and gynecological outcomes?

SUMMARY ANSWER: We did not observe an increase of obstetric or gynecological problems after fetoscopic surgery nor was there an increased risk for subsequent infertility.

WHAT IS KNOWN ALREADY: The reproductive and gynecological outcomes of patients undergoing open maternal-fetal surgery are known. The most relevant counseling items are the elevated risk for uterine dehiscence and rupture (up to 14%).

STUDY DESIGN, SIZE, DURATION: Bi-centric study over a 10-year period including 371 women carrying a fetus with isolated CDH either managed expectantly ($n = 167$) or operated *in utero* ($n = 204$).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Consenting patients filled out a survey with 23 questions (2 open and 21 multiple choice). Questionnaires were custom designed to obtain information on subsequent reproductive or gynecological problems as well as psychological impact.

MAIN RESULTS AND THE ROLE OF CHANCE: The response rate was 40% (147/371). More women in the FETO group attempted a subsequent pregnancy: 70% (62/89) when compared with 47% (27/58) in controls ($P = 0.009$). This coincided with a longer follow-up in the FETO group (76 versus 59 months; $P < 0.001$) and a lower survival rate in the index pregnancy (53 versus 72%; $P = 0.028$). There was no difference in the number of nulliparous or parous women, neither in the conception rate. In total, there were 129 subsequent pregnancies. Nobody reported secondary fertility problems. Four women in the FETO group and one in the control reported a congenital anomaly in a subsequent pregnancy. Twenty-one pregnancies were reported with at least one complication (FETO: 23% (14/60), controls 27% (7/26)). During delivery or in the post-partum period 11 patients reported at least 1 complication (FETO 17% (10/59), controls 4% (1/24)). New onset gynecological problems occurred in 14 participants (10%). None of these events were more likely in one or the other group. Psychological and emotional impacts were frequent in both the FETO (41%) and the control groups (46%) ($P = 0.691$).

LIMITATIONS, REASONS FOR CAUTION: The response rate was 40% (147/371), less than desired. The use of unvalidated self-reported outcomes may skew exact determination of the nature and severity of medical complications. The number of observations for uncommon events was low. The mean follow-up period to detect gynecological complications may be too short.

WIDER IMPLICATIONS OF THE FINDINGS: This is the first evidence that fetoscopic surgery for CDH does not compromise future reproductive potential or obstetrical outcome when compared with expectant management. A pregnancy complicated by a serious congenital birth defect, such as CDH, frequently has a measurable psychological impact.

STUDY FUNDING/COMPETING INTEREST: The authors have no conflicts to declare. J.D. receives a fundamental clinical research grant of the Fonds Wetenschappelijk Onderzoek - Vlaanderen (FWO; 18.01207). A.C.E. is supported by the Erasmus+Program of the European

Union (Framework agreement number 2013-0040; contract 1011990). This was presented at the 61st meeting of the Society of Gynaecologic Investigation, in Florence, March 2014 (F-111).

Key words: congenital diaphragmatic hernia / fetal surgery / fetal endoscopic tracheal occlusion / fertility / pregnancy outcome / gynecological outcome / psychological outcome

Introduction

Congenital diaphragmatic hernia (CDH) is a rare condition with a prevalence of approximately 1/2500–1/5000 births (Colvin *et al.*, 2005). In the majority of cases, the defect is located on the left (84%), 13% are right sided and 2% are bilateral (Torfs *et al.*, 1992). In 40%, the defect is associated with other congenital malformations with poor prognosis in those cases (Skari *et al.*, 2000). Current survival rates in population-based studies vary between 55 and 70% (Jani *et al.*, 2005). Survivors may have serious morbidity, mostly respiratory in nature as well as feeding problems and reflux, growth and orthopedic problems. The leading causes of death remain pulmonary hypoplasia and pulmonary hypertension (Laberge and Flageole, 2007). *In utero* transfer to specialized, high-volume centers has a significant impact on survival (Gallot *et al.*, 2007; Deprest *et al.*, 2011). In isolated CDH, the outcome correlates with the degree of pulmonary hypoplasia and the position of the liver. Whether these are independent predictors remain controversial. Both can be measured by noninvasive imaging methods, such as ultrasound and fetal magnetic resonance (Metkus *et al.*, 1996; Claus *et al.*, 2011).

Based on a severity assessment, fetal therapy can be offered to subgroups that have a poor predicted outcome. Currently, this is by fetoscopic endoluminal tracheal occlusion (FETO), which involves the percutaneous insertion of a balloon into the trachea. It prevents egress of lung fluid, inducing growth of the lung by tissue stretch (Deprest *et al.*, 1998; Khan *et al.*, 2007). FETO apparently increases survival in fetuses with CDH and severe pulmonary hypoplasia (Jani *et al.*, 2009) and also improves early neonatal morbidity (Done *et al.*, 2013, 2015). At this moment, the efficacy of prenatal intervention is being investigated in the so-called TOTAL randomized clinical trial (www.totaltrial.eu) that compares neonatal outcomes after FETO or expectant management (Jani *et al.*, 2005; Dekoninck *et al.*, 2011).

Fetal surgery for other conditions is also possible through open access, involving general anesthesia, laparotomy and hysterotomy (referred to as 'open' maternal-fetal surgery (OMFS)). Maternal risks include surgical bleeding, pulmonary edema, infection, preterm rupture of membranes, preterm labor and delivery and, when applicable side effects of medical therapies, e.g. aggressive tocolysis. Either access method (percutaneous or open) for fetal surgery, may have long-term risks for the mother. The reproductive and gynecological outcomes of patients undergoing OMFS have been reported by Wilson *et al.* (2004, 2010).

They included all their patients undergoing OMFS presenting with CDH, myelomeningocele, lethal lung malformations and sacrococcygeal teratoma. They did not observe an increase in the prevalence of congenital anomalies or fertility problems. However, they did observe a significance incidence of uterine dehiscence (14%) and rupture (14%) (Wilson *et al.*, 2004, 2010).

Such outcome data on endoscopic fetal surgery as far as we are aware have not been reported. In this study, we aimed to document reproductive, obstetrical and gynecological outcomes and psychological impact in women who underwent fetoscopic surgery for CDH at two institutions. This knowledge is valuable in the counseling of future families when faced with a severe fetal anomaly such as CDH, who would consider fetal surgery or participation to the TOTAL trail (Dekoninck *et al.*, 2011).

Materials and Methods

This was a bi-centric cohort study conducted at the fetal medicine units of the University Hospitals Leuven and Hospital Clínic Barcelona spanning a 10-year period from 2002 onwards. The study was approved by the local Ethics Committees on clinical studies. We searched our database for all women who were prenatally diagnosed with CDH without associated structural or genetic anomalies. Women who requested termination of pregnancy or in whom the diagnosis of nonisolated CDH was made in the post-natal period were excluded. The minimum follow-up period following birth in the index pregnancy was 1 year at the start of the study. Our search resulted in 371 eligible patients. These were categorized as either expectantly managed during pregnancy (controls) or as having undergone fetal surgery (FETO group). The latter patients by definition had a fetus with severe lung hypoplasia. The controls overall had milder hypoplasia, or, in case of severe hypoplasia, declined fetal surgery. Therefore, severity of hypoplasia, hence expected pregnancy outcome, should be worse in the FETO group. First, all woman received written information concerning the purpose and description of the study and an informed consent form. Of those patients with whom we had email contact, this was done via email; the other patients received the same information by standard mail.

Once consenting, participants were offered two options to fill out the questionnaire, either via Limesurvey (v. 2.00+, The LimeSurvey Project Team, GPL); or, alternatively, via a printed questionnaire to be returned in a prepaid envelope. The questionnaire we used was based on the one designed by Wilson *et al.* (2004, 2010) and previously used in patients undergoing OMFS (Supplementary data). Though that questionnaire is not formally validated their work is considered unique and represents a landmark study. We supplemented it with an additional five questions assessing gynecological problems. Briefly, participants were asked to self-report the occurrence of reproductive, obstetric, gynecological, psychological and/or emotional problems since their index pregnancy. In total, the questionnaire covered 23 items, i.e. 21 multiple choice and 2 open questions (Supplementary data). Questions 1–4 documented the interval between index and further pregnancy attempts; in the case of no further attempts, the patient was asked in an open question if there was any relationship of that decision to her previous complicated pregnancy or with the disease process in the index child. For those who attempted further conception, Question 5–15 were concerned with fertility issues, and when pregnant, for miscarriage, pregnancy complications, preterm labor, preterm rupture of the membranes, uterine rupture, placentation problems or post-partum hemorrhage. Question 16 asked participants for any potential emotional and psychological problems, leaving the participants to describe their nature in open Question 17. Questions 18–23 asked for the occurrence of new gynecological problems or abdominal pain. The questionnaire was available in Dutch, French,

English, Spanish and Italian, languages spoken or understood by the patients managed.

The medical records of all invited patients were searched for maternal age, parity prior to the index pregnancy, as well as its further management and outcome, including whether they had fetal surgery.

Statistical analyses

The answers from participants were linked to the data of the medical records, pooled in a Microsoft Excel database (Microsoft Corp, Redmond, WA, USA) and analyzed with SPSS (Vs. 20; IBM Software, Inc., Armonk, NY, USA). Normality tests were used to determine distribution. Demographic data are displayed by using descriptive statistics such as number, percentage, mean, standard deviation (SD), median, interquartile range (IQR) and range as appropriate. Categorical variables were analyzed by the Pearson χ^2 test. The numerical variables were analyzed with a two-sided *t*-test. A *P*-value of <0.05 was considered significant for each analysis.

Results

Of the 371 patients contacted, 204 patients had fetal surgery (FETO group). There were 167 women who were expectantly managed during pregnancy (controls), either because severity of lung hypoplasia was moderate or mild, or, in case of severe hypoplasia, they did not opt for FETO. The age of invited patients at baseline in Leuven was 2 years less than in Barcelona. The interval between the index pregnancy and the survey was 17 months longer in Leuven, which coincides with the later adoption of FETO in Barcelona. There were no differences in parity or survival rate in the index pregnancy.

The overall response rate was 40%. The only statistically significant difference between participants and nonparticipants was the interval between the index pregnancy and survey, which was 7 months shorter in nonparticipants (Table I). The response rate was comparable among FETO patients (44%, 89/204) and controls (35%; 58/167, $P = 0.102$).

Table II displays data from the 147 consenting participants of whom 89 underwent fetal surgery (cases) and 58 were controls. More women in the FETO group attempted a subsequent pregnancy (70% (62/89) versus 47% (27/58) in controls; $P = 0.009$). This coincided with a longer duration of follow-up in the FETO group (76 versus 59 months; $P < 0.001$). Also the survival rate in the index pregnancy was lower in the FETO group (53 versus 72%; $P = 0.028$). We did not observe a difference in number of nulliparous or parous women.

Table I Demographic variables and pregnancy outcomes in participants and nonparticipants.

	Nonparticipants	Participants	*P*-Value
FETO ($n = 204$)	115 (56%)	89 (44%)	0.102
Controls ($n = 167$)	109 (65%)	58 (35%)	
Mean age at index pregnancy (years)	30.5 ± 6.3	31.1 ± 5.9	0.312
Parity at baseline			
0	93 (50%)	67 (53%)	0.720
≥1	93 (50%)	60 (47%)	
Neonatal death in index pregnancy	49%	39%	0.083
Mean age at survey (years)	35.7 ± 6.5	36.8 ± 6.2	0.069
Mean interval index pregnancy to study invitation (months)	62.5 ± 30.3	69.1 ± 30.1	0.042

FETO, fetoscopic endoluminal tracheal occlusion.
Data are the pooled data from both centers and are *n* (%) or mean ± SD.

In total, there were 129 subsequent pregnancies in 82 women (Table II and Fig. 1). Three participants became pregnant by Assisted Reproductive Technology (ART); however, we noted they required ART previously. Therefore, no new onset fertility problems were identified in our responding cohort. The chance of conception did not differ between both groups (FETO 94%, 58/62 and controls 89%, 24/27, $P = 0.43$). There were no differences in first trimester pregnancy losses. There were no early mid-trimester losses, and the number of preterm deliveries was not different. There were few medical problems in gestation. One hundred and five women delivered at a viable gestational age. In 21 of these pregnancies the patient reported 1 or more complications, yet this was not more likely in FETO than control patients ($P = 0.934$). Pregnancy outcomes are further detailed in Table II. There were 11 post-partum complications. No participants from the FETO group reported any uterine scar-related complications like dehiscence or rupture. Five babies had congenital anomalies.

Overall, 82% of patients of whom the baby died attempted to conceive again versus 48% in mothers who had a surviving baby in the index pregnancy. Fifty-eight women did not wish to conceive again (FETO 30%, 27/89; controls 53%, 31/58; $P = 0.009$). Of those, 19 (33%, 19/54) mentioned that this decision was related to the congenital anomaly in the index pregnancy. For those 19 women, there was no difference in management of the index pregnancy (FETO 22%, 6/21, controls 42%, 13/18; $P = 0.189$). They reported as reasons fear for recurrence (10/19 patients), psychological distress persisting since the CDH-pregnancy (6/19) or current and past health problems in the baby with CDH (5/19). The neonatal death rate in the index pregnancy of these 19 patients was 11%, whereas it was 21% in the 39 patients who did not wish to conceive, yet did not mention the index problem as the reason for that ($P = 0.474$).

Table III summarizes the psychological problems following the index pregnancy, as quoted by respondents, irrespective of the further wish for conception. Reports of psychological and emotional impact were frequent (43%, 61/141), yet equal in both groups. The most frequent psychological problems were anxiety ($n = 19$) and depressed mood ($n = 12$). Fourteen women (10%, 14/141) reported new gynecological problems, mostly abnormal uterine bleeding ($n = 7$), and chronic abdominal pain ($n = 8$) (Table III). Again, none of these were more frequent in one or the other group.

We did an additional analysis to evaluate the impact of neonatal death in the index pregnancy on the prevalence of psychological problems. When considering only the respondents with psychological problems, the likelihood of a nonsurviving baby in the index pregnancy was higher in FETO patients than in controls, paralleling what was already observed among all participants (Table III).

Discussion

We did not observe differences in subsequent fertility, pregnancy and gynecological outcomes in patients with fetuses with severe CDH who had either fetoscopic surgery or who were expectantly managed

Table II Essential baseline data and subsequent pregnancy outcomes in study participants treated by fetoscopic endoluminal tracheal occlusion (FETO) or expectant management (Control).

	FETO	Controls	*P*-Value
n (%)	89 (44%)	58 (35%)	
Interval between index pregnancy and survey (months)	75.6 ± 31.38	59.0 ± 24.89	<0.001
Previous obstetrical history at baseline			
Parity at index pregnancy[a]			
0	40 (47%)	27 (64%)	0.101
≥1	45 (53%)	15 (36%)	
Survival of CDH fetus in index pregnancy	53%	72%	0.028
Subsequent pregnancies			
Further attempt to conceive	62 (70%)	27 (47%)	0.009
Of those attempting to conceive			
Patients with 0 subsequent pregnancies	4 (6%)	3 (11%)	0.430
Patients with ≥1 subsequent pregnancies	58 (94%)	24 (89%)	
Requiring for the first time ART	0 (0%)	0 (0%)	
Number subsequent pregnancies in all patients	90	39	
No further attempt to conceive	27 (30%)	31 (53%)	0.009
Of those, related to the index pregnancy	6 (22%)	13 (42%)	0.188
Subsequent pregnancy outcome			
Gestational age at delivery[b]			0.957
Miscarriage (loss <20 weeks)	12 (14%)	8 (22%)	
Pregnancy loss 20–24 weeks	0 (0%)	0 (0%)	
Delivery 24–28 weeks	0 (0%)	0 (0%)	
Delivery 28–37 weeks	7 (8%)	2 (5%)	
Delivery 37 weeks plus	69 (78%)	27 (73%)	
Cumulative number of pregnancies with at least one of the following complications during pregnancy[c]	14 (23%)	7 (27%)	0.934
Exact numbers of pregnancies complicated with			
Diabetes	5	4	
Hypertension	4	1	
Bleeding during pregnancy	2	3	
Others[f]	4	1	
Cumulative number of pregnancies with at least one of the following complications at delivery or thereafter[d]	10 (17%)	1 (4%)	0.230
Exact numbers of pregnancies with			
Hemorrhage at or immediately after delivery	4	0	
Preterm labor and/or preterm rupture of the membranes	5	1	
Others[g]	1	0	
Birthweight (kg)	3.39 ± 0.48	3.37 ± 0.38	0.810
Delivery mode[e]			
Vaginal delivery	43 (60.5%)	22 (81%)	0.086
Cesarean delivery	28 (39.5%)	5 (19%)	

All percentages in the above table are calculated on patients with known data.
Data are mean ± SD or *n* (%).
For some parameters there were missing data:
[a]Parity in the index pregnancy (FETO: 4; Controls: 16).
[b]Gestational age at delivery (FETO: 2; Controls: 2).
[c]Pregnancy complication(s) (FETO: 16; Controls: 3).
[d]Complications at delivery or thereafter (FETO: 17; Controls: 5).
[e]Delivery mode delivering >24 weeks (FETO: 5; Controls: 2) and unknown term at the end of pregnancy (FETO: 2; Controls: 2).
[f]Other complications during pregnancy FETO: placenta previa, cytomegalovirus infection in mother, placenta problem not otherwise specified, need for the use of low molecular weight heparin not otherwise specified. In controls: hypothyroidism.
[g]Complications at delivery or thereafter FETO: manual removal of placenta.

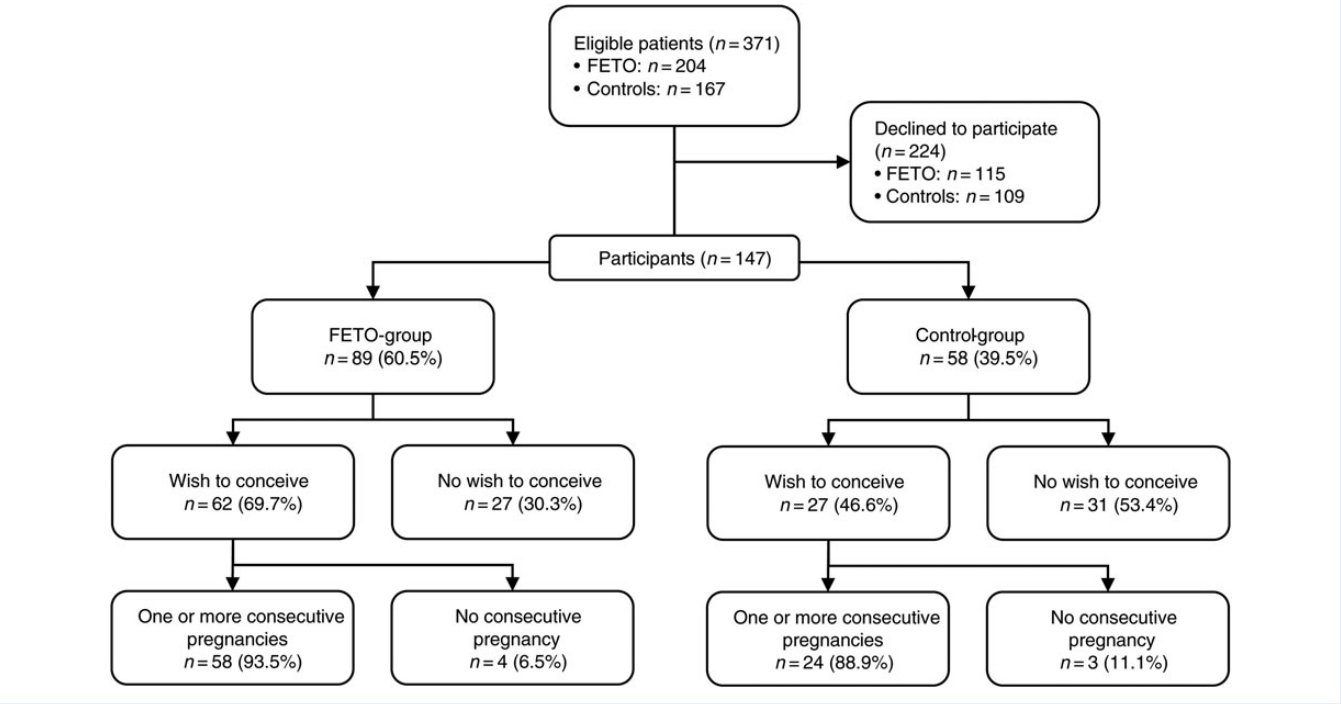

Figure 1 Flow diagram of the subsequent attempts to conceive after treatment by fetoscopic endoluminal tracheal occlusion (FETO) or expectant management (Control).

during the index pregnancy. Though persisting psychological problems were frequent, they were not more common in the fetal surgery patients. In woman who had fetal surgery in the index pregnancy, persistent psychological impact coincided with a poorer neonatal outcome.

Fetal surgery essentially implies an intervention in an otherwise healthy mother. This may cause complications and side effects during the index pregnancy, but theoretically it may also impact later reproductive life. There is only limited data available on medium or long-term maternal outcome after OFMS, though OFMS is already practiced for more than 20 years. Fetoscopy has been utilized since the late 90s yet no long or medium term outcomes were so far reported (Wenstrom and Carr, 2014). In this study, we did not observe an adverse impact of fetoscopic surgery on the wish to conceive. This is in line with what has been observed for OMFS (Wilson *et al.*, 2004, 2010). Conversely, there were significantly more women attempting a further pregnancy after FETO. This may have several reasons. There were significantly less survivors in the index pregnancy in FETO patients, what is in line with the more severe nature of pulmonary hypoplasia in that group. Also, the mean follow-up was 17 months longer in the FETO group than in controls, which could also result in identification of more women wanting to conceive again.

One out of the three patients who did not wish to conceive, specifically related their decision to events in the index pregnancy. This was independent of the nature of the management of the index pregnancy. The average perinatal outcome of subsequent pregnancies was not different in participants having undergone FETO or those expectantly managed. Neither were there more pregnancy nor post-partum complications in FETO participants than controls.

Though the number of patients is limited, not a single mother who conceived after FETO reported problems with the uterine scar. This is in contrast to what is reported for OMFS, where the former hysterotomy is considered as a potential weak location prone to dehiscence and/or rupture. Because of the risk for uterine rupture during pregnancy or labor, those women are advised to deliver by elective repeat Cesarean delivery at ~37 weeks. This is based on relatively striking rates of uterine dehiscence (14%), rupture (14%) and Cesarean hysterectomy (3%) in the experience reported by the Children's Hospital of Philadelphia (Wilson *et al.*, 2004, 2010). These dehiscence and rupture numbers are in the range of what is reported after classical Cesarean delivery (Wilson *et al.*, 2010). Conversely, we did not see any such events in our FETO patients, who in 61% of cases delivered later vaginally.

A large percentage of woman (43%) reported later psychological or emotional problems, yet there was no difference between the operated and conservatively managed groups. Psychological problems in women who carried and/or delivered a fetus with a severe congenital malformation have been often described, but none of these studies included patients undergoing fetal therapy. In our study, the psychological burden of the index pregnancy and decision to pursue fetal surgery compounds the existing maternal psychological adjustment required during pregnancy. Carrying a fetus or delivering a neonate with a congenital anomaly should therefore not be underestimated. Our data should prompt pre-emptive measures to organize prospective support during and after the index pregnancy (Leithner *et al.*, 2004; Aite *et al.*, 2009). In the FETO group, there was a relation between the survival of the baby in the index pregnancy and the prevalence of psychological problems. Significantly, more women reported emotional problems when

Table III Psychological and gynecological outcomes in study participants treated by fetoscopic endoluminal tracheal occlusion (FETO) or expectant management (Control).

	FETO	Controls	*P*-Value
Self-reported psychological outcome			
Cumulative number patients reporting psychological problems in the index pregnancy (%)[a]	36 (41%)	25 (46%)	0.691
Ending with survivor	37%	72%	0.016
Ending with nonsurvivor	63%	28%	
Depressed mood	9	3	
Anxiety concerning health of the baby, fear for repetition	13	6	
Relational problems, related to the events in index pregnancy/anomaly	2	4	
Impaired perception of the subsequent pregnancy	3	1	
Feelings of guilt	3	0	
Others unclassified problems	10	7	
Self-reported gynecological outcome			
Cumulative number patients reporting gynecological problems (%)[b]	8 (9%)	6 (11%)	0.982
Abnormal bleeding	5	2	
Abdominal pain	5	3	
Others	1[c]	2[d]	

[c]Pelvic floor dysfunction.
[d]Benign ovarian cyst, conization.
Percentages where calculated on known data: missing data:
[a]Psychological problems (FETO 2, Controls 4).
[b]Gynecological problems (FETO 3, Controls 3).

their baby died. This was not observed in the control group. Obviously this may be due to fetal surgery itself, yet may as well be explained by the higher likelihood of post-natal death in the fetal surgery patients, who have a poorer prognosis.

This study has a number of weaknesses. First, we used no condition specific validated questionnaires. In their absence, we modified the only questionnaire available. This questionnaire was designed to specifically ask about obstetrical outcomes that could theoretically be altered by the fetal surgical procedure (Wilson *et al.*, 2004, 2010). Using very similar questionnaires we think that making a comparison with OFMS is reasonable. Regardless, both our study and those ones on OMFS patients could not detect an adverse impact of fetal surgery on subsequent pregnancy, fertility and gynecological outcomes. This use of an unvalidated instrument should be taken into account interpreting the results. The assessment of the long-term psychological impact using validated instruments is an interesting subject for further research. Another limitation is the relative low response rate (40%), which was lower than what Wilson *et al.* described (57%). Another generic limitation is that we used self-reported outcomes. This may lack accuracy for precise determination of the occurrence, nature and severity of some medical complications. Also for some rarer complications the number of events was very low or zero, eventually making a statistical comparison virtually meaningless. Finally, the mean follow-up period of only 5.8 years and a mean age of around 37 years when being polled, may lead to an underestimation of subsequent gynecological problems, which typically occur later in life.

The strength of this study is that it is the first reporting on reproductive outcomes following fetoscopic surgery using an appropriate control group. Though numbers are small, indications for fetal surgery are limited such large data sets are not easily obtained, and we use comparable numbers of patients to previous studies. Despite the limitations, it seems reasonable to conclude that fetoscopic surgery for CDH does not seem to have adverse maternal effects on the medium term, yet most of the impact seems to be due to the burden of a severe congenital birth defect (Leithner *et al.*, 2004; Aite *et al.*, 2009).

Conclusion

In this controlled study, we did not observe a relevant impact of fetal surgery for CDH on future fertility, obstetrical and early gynecological outcomes. A significant number (43%) of participants reported a serious psychological impact of the index event, irrespective of its management during pregnancy.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors' roles

C.G. and J.A.D.: substantial contributions to the design, acquisition, analysis and interpretation of data of this study. A.C.E., P.D.K., L.L. and E.G.: substantial contributions to the design of this study. Critical revising of the article. O.G.: substantial contributions to the acquisition of the data.

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Conflict of interest

None declared.

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SUPPLEMENTARY DATA

Pregnancy desire

1 Have you attempted to get pregnant again after your pregnancy in which a congenital diaphragmatic hernia was detected?

- ○ Yes (Proceed to question 4)
- ○ No (Proceed to question 2)

2 Is there any relationship between the problem in your previous pregnancy or the pregnancy outcome and the fact that you haven't attempted for a new pregnancy?

- ○ Yes (Proceed to question 3)
- ○ No (Proceed to question 20)

3 If so, are you willing to summarize the reason why you haven't attempted for a new pregnancy?

4 How much time was there in between the delivery, of the pregnancy with a congenital diaphragmatic hernia, and a new attempt to get pregnant?

[ ] Months (Proceed to question 5)

Pregnancy outcomes

We would like to investigate if there were any problems or complications during one of these pregnancies. We would like you to answer the following questions separately for the first three pregnancies after the pregnancy in which a congenital diaphragmatic was detected.

5 Was it a singleton, twin or triplet?

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
Singleton	○	○	○
Twin	○	○	○
Triplet	○	○	○

6 What was the estimated gestational age at the moment of delivery? (the normal gestational age is 40 weeks)

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
Miscarriage or loss at less than 20 weeks	○	○	○
20-24 weeks	○	○	○
24-28 weeks	○	○	○
28-36 weeks	○	○	○
> 37 weeks	○	○	○

7 The delivery was

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
Vaginally	○	○	○
Caesarean Section	○	○	○

8 What was the birth weight of your child? (in kilogram)

	First Pregnancy after your surgery	Second Pregnancy after your surgery	Third Pregnancy after your surgery
What was the birth weight of your child? (In kilograms)	.....	.....	.....

9 Was there any congenital anomaly/malformations?

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
Yes	○	○	○
No	○	○	○

10 If yes, what kind of anomaly?

11 Where there any problems/complications during your pregnancy?

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
Bleeding during your pregnacy	☐	☐	☐
Placenta problems	☐	☐	☐
High blood pressure/Pre-eclampsia	☐	☐	☐
Diabetes of pregnany (gestational)s	☐	☐	☐
Others	☐	☐	☐

12 Specify others.

13 Where there any problems/complications during labour or delivery?

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
The water broke too early (more than 24 hours before labour)	☐	☐	☐
Labour occurred too early (before 8 months/37weeks)	☐	☐	☐
Excessive blood loss during delivery	☐	☐	☐
Problems with the uterine scar of the previous fetoscopic surgery	☐	☐	☐
Others	☐	☐	☐

14 Specify others.

15 May we contact your gynecologist to provide us detailed information about these problems?

- ○ Yes (Proceed to question 16)
- ○ No (Proceed to question 17)

16 Could you please give us the name and address of your gynecologist?

- Name.....
- Address.....
- tell/email address.....

17 Did you get spontaneously pregnant, i.e. without medical help?

	First Pregnancy after your surgery	Second pregnancy after your surgery	Third pregnancy after your surgery
Yes	○	○	○
No	○	○	○

18 If there are fertility problems, did they exist before the pregnancy in which a congenitale hernia diafragmatica was detected?

- ○ Yes
- ○ No

19 What type of assisted reproduction techniques did you require?

- ☐ Medication to stimulate ovulation
- ☐ Artificial insemination
- ☐ IVF (In Vitro Fertilization)/ ICSI (Intracytoplasmic sperm injection)
- ☐ Use of donor sperm and/or female egg (oocyte).

Psychological problems

20 Have you had any psychological or emotional problems related to congenital disorder of your baby or the pregnancy outcome?

- ○ Yes (Proceed to question 21)
- ○ No (Proceed to question 22)

21 Could you please describe them?

Gynecological Problems

22 Have you had any new gynecological problems after your pregnancy with a congenital diaphragmatica hernia?

- ○ Yes (Proceed to question 23)
- ○ No (The survey ends here for you)

23 Did you had abnormal menstruations after your surgery

- ○ Yes
- ○ No

24 How many months after your surgery did this problem start?

Months

25 What was the cause of this bleeding as declared by your gynecologist or general practitioner?

26 Did you have a lot of lower abdominal pain after your surgery?

- ○ Yes
- ○ No

27 How many months after your surgery did this pain start?

Months

28 What was the cause of this pain as declared by your gynecologist or general practitioner?

29 Do you have any other gynecological problem since your surgery?

- ○ Yes
- ○ No

30 How many months after your surgery did these problems start?

Months

31 Which problem is it and what was the cause as declared by your gynecologist or general practitioner?

32 May we contact your gynecologist to provide us detailed information about these problems?

- ○ Yes
- ○ No

33 Could you please give us the name and address of your gynecologist?

- Name.....
- Address.....
- tell/email address.....

Thank you very much for your participation.